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## (54) Glycyrrhetinic acid derivatives and antiviral compositions thereof.

(57) Glycyrrhetinic acid substituted at its 30 positions is of the general formula

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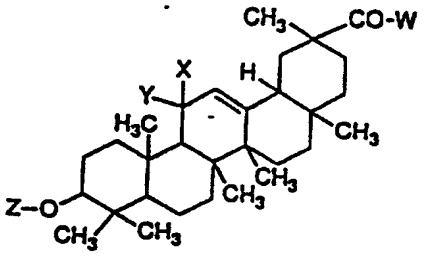


... (I)

where X and Y are H or together oxo, Z is a saccharide or $-A_2-(CH_2)_n-(CH=CH)_m-A_1-$ and W is extensively defined, including of three further general formulae each terminating in substituted phenylpiperazine.

Synthesis can be by use of a glycosyl bromide and a condensing agent and optionally sulfation or phosphation.

The compounds and their salts have antiviral action, especially those which contain as the aglycon a 4-(substituted)phenylpiperazine-1-yl derivative.

Pharmaceutical compositions are described for oral, topical or injection administration.

The compounds and compositions are effective to treat viral diseases, e.g. herpes virus or influenza.

The present invention relates to novel glycyrrhetinic acid derivatives which can be used as the main active components of medicaments for the prophylaxis and treatment of virus infections.

Glycyrrhetinic acid and certain derivatives thereof known to have anti-ulcer, anti-inflammatory, antiallergic, anti-hepatitis and antiviral actions. Among such compounds known so far in the art, for instance, there are carbenoxolone (U.S. Patent No. 3070623), glycyrrhetinic acid ester derivatives having substituents at the 30-positions (U. S. Patent No. 3070624), amino acid salts of glycyrrhetinic acid (Japanese Patent Publication JP-A-44-32798), amide derivatives of glycyrrhetinic acid (Belgian Patent No. 753773), amide derivatives of 11-deoxoglycyrrhetinic acid (British Patent No. 1346871), cicloxolone ("Journal of Antimicrobial Chemotherapy", Vol 18, Suppl. B, pp. 185-200 (1986)), and glycyrrhizic acid and its derivatives ("Chem. Pharm. Bull.", 39(1), pp. 112-115 (1991)). Apart from these, we have also devised a novel method of synthesizing 11-deoxoglycyrrhetinic acid (Japanese Patent Laid-Open Publication JP-A-59-70638) as well as its hemiester derivatives (Japanese Patent Laid-Open Publication JP-A-58-8044) and its carboxylic acid and amide derivatives (Japanese Patent Laid-Open Publication JP-A-63-135351).

As already noted, glycyrrhetinic acid and its derivatives have a variety of useful pharmacological actions. Never until now, however, is there any report that they have an antiviral action well enough for therapy. In addition, they have some serious problems, e.g., they show cytotoxicity in tests where they are used at concentrations high enough to achieve antiviral activity, they are unstable in aqueous solutions, and so on.

In recent years, other antiviral agents based on nucleic acid, which is represented by acyclovir, have been developed and found to be clinically efficacious against herpes virus infections in particular. However, another problem has arose in connection with resistance virus (e.g., thymidine kinase negative one) infections ("Oral. Surg. Oral. Med. Oral. Pathol", Vol. 67, pp. 427-432 (1989)). These nucleic acid type antiviral drugs have also generally been known to be ineffictive against RNA virses represented by influenza virus. In addition, it has been pointed out that they have some therapeutic effects in pill or injectable forms, but they are not or little efficacious when applied to the site of infection as ointment ("Antiviral Research", Vol. 14, pp. 305-321 (1990)).

Among antiviral agents other than the nucleic acid type antiviral agents and efficacious against DNA viruses, for instance, phosphonoformate (PFA for short; see "Nippon Rinsho", Vol. 47 (2), pp. 390-394 (1989)), phosphonoacetate (PAA for short; see "Nippon Rinsho", Vol. 47 (2), pp. 390-394 (1989)) and cicloxolone ("Journal of Antimicrobial Chemotherapy", Vol. 18, Suppl. B. pp. 185-200 (1986)) have been known. However, problems with phosphonoformate and phosphonoacetate are that they have side effects such as renal disorders and anemia, whereas cicloxolone does not have an antiviral activity high enough for therapy.

Among another group of antiviral agents other than the nucleic acid type antiviral agents and efficacious against RNA viruses, for instance, amantadine ("Shonika Sinryo", Vol. 54(4), pp. 988-994 (1991)), remantadine ("Shonika Sinryo", Vol. 54(4), pp. 988-994 (1991)) and LY253963 (a thiadiazol derivative; "Shonika Sinryo", Vol. 54(4), pp. 988-994 (1991)) have been known. Amantadine and remantadine have been shown to be efficacious against influenza A virus but not against influenza B virus, and pose a grave problem - a side effect on the central nerve. LY253963 has been shown to be resistant to influenza viruses in animal tests, but its clinical efficacy has yet to be verified.

Recent knowledge of the gene structure of hepatitis C virus (HCV) that is a leading cause of post-transfusion hepatitis has indicated that it is a single stranded RNA virus having a full length of about 9.5 kilobases ("Science", Vol 244, pp. 359-362 (1989)). However, because HCV is a virus very likely to mutate and is not well clarified in terms of how it replicates, the development of vaccines or anti-HCV drugs is still very slow ("Shindan To Tiryo", Vol. 80 (2), pp. 295-302 (1992)).

For instance, AZT and DDI have been known as antiviral agents efficacious against retroviruses represented by AIDS virus (HIV) ("Shonika Shinryo", Vol. 54(4), pp. 981-987 (1991)). However, these agents delay the development of AIDS, but cannot accelerate healing and have severe side effects such as myelopathy as well.

In recent years, the occurence of immunodeficiency diseases induced by organ transplantation, cancer chemotherapy and HIV infections has increased, posing a grave medical problem. Virus infections in such patients are so diverse in type that they often cannot be treated with existing antiviral drugs. Thus, much is now expected of the development of more improved antiviral drugs and also of more efficacious antiviral drugs for HIV and HCV.

It is therefore a primary object of this invention to provide a novel glycyrrhetinic acid derivative which has an excellent antiviral action on various DNA viruses, RNA viruses and retroviruses inclusive of acyclovir-resistant herpes virus, HIV and HCV, and an antiviral agent containing the glycyrrhetinic acid derivative as the main component.

We have first studied glycyrrhetinic acid derivatives to find their possibility of being used as anti-ulcer and - inflammatory drugs but, in the course thereof, we fortuitously discovered that compounds having various substituents at the 30-positions of glycyrrhetinic acid or its derivatives have an excellent antiviral activity. Among them, a compound having a phenylpiperazine derivative at the 30-position of glycyrrhetinic acid or its derivative,

i.e., 1-[3β-(3-carboxypropanoyloxy)-18β-olean-12-en-30-yl]-4-(2-methoxyphenyl) piperazine, has been found to have a particularly high antiviral activity and be of great safety.

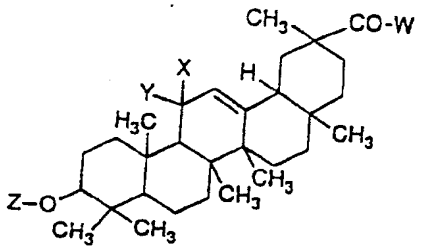
With a view to revealing the significance of phenylpiperazine or its related compounds bonded as substituents to the 30-positions of glycyrrhetinic acid or its derivatives, we have studied the antiviral and cytotoxic actions of modified or unmodified phenylpiperazine, phenylpiperidine, phenylpyrrolidine, phenyltetrahydroimidazole, phenylhomopiperazine, phenylaziridine, phenylazetidine, phenyldiazetidine and phonylporhydroazepine Surprisingly enough, we have discovered that a number of compounds have a wide spectrum of antiviral actions on various DNA and RNA viruses, like herpes simplex virus (types 1 and 2), vaccinia virus, cytomegalovirus, influenza virus, hepatitis B virus and AIDS virus, and provide efficacious drugs for both topical and systemic therapies.

We have then investigated the antiviral activity of known compounds containing the above-mentioned modified or unmodified phenylpiperazine and its related compounds as substituents in their structures and novel compounds into which these compounds are introduced as substituents. Interestingly enough, we have thus discovered that many compounds have strong antiviral actions.

Based on such findings as mentioned above, we have strenously made intensive studies to achieve more improved antiviral activity than ever before. Consequently, we have discovered that compounds, which have saccharides at the 3-position of glycyrrhetinic acid or its derivatives and modified or unmodified phenylpiperazine or its related compounds at the 30-position thereof, have very excellent antiviral actions and, at the same time, reduced or limited cytotoxic actions. This finding underlies the present invention.

This invention provides novel glycerrhetinic acid derivatives having the following general formula (I).

General Formula (I)

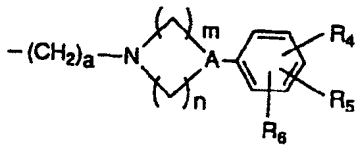



wherein

X and Y each represent a hydrogen atom or forms together an oxo group,

Z represents $A_2$-$(CH_2)_n$-$(CH{=}CH)_m$-$A_1$-, wherein $A_1$ means a hydrogen atom or methylene or carbonyl, and $A_2$ means a hydrogen atom, a cyano group, a carbamoyl group, a carbonyl group or an alkoxycarbonyl group, m represents zero or an integer of 1-3, and n represents zero or an integer of 1-5, or a monosaccharide, disaccharide, oligosaccharide or polysaccharide or their derivative, and

W represents a substitutent expressed by -$OR_1$ where $R_1$ means a hydrogen atom, an alkyl, substituted alkyl or substituted alkenyl group, or a group having the following general formula (II)

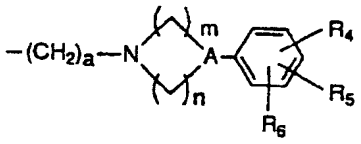



... (II)

wherein A means a nitrogen atom or a methyne or methylene group, and $R_4$, $R_5$ and $R_6$ concurrently or independently mean a hydrogen atom, an amino group, an optionally substituted alkylamino group, an acylamino group, an optionally substituted alkyl group, a hydroxy group, an optionally substituted alkyloxy group, a halogeno group, a carboxy group, a formyl group, an optionally substituted alkylcarbonyl group, an optionally substituted alkoxycarbonyl, an aryloxycarbonyl group, an optionally substituted carbamoyl group, a nitro group, a cyano group, a thiol group, an optionally substituted alkylthio group, an optionally substituted phenyl group or

an optionally substituted heterocycle m represents 0 or any desired integer, a and n each represent any desired integer, provided that the term "optionally substituted" means that said groups may be substituted by groups selected from amino, formyl, hydroxy, alkoxy, aryloxy, halogeno, nitro, cyano, thiol, alkylthio, arylthio, acyl, carbamoyl, alkylsilyl, arylsilyl, alkyloxycarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfinyl and arylsulfinyl groups, such acid groups as phosphoric, phosphonic, phosphinic, phosphenic, sulfonic, sulfinic, sulfuric and boric acid groups or their esters, and the term "heterocycle" means pyridine, piperidine, piperazine, pyrrole, pyrrolidine, oxazole, imidazole, morpholine, diazole, triazole, tetrazole, thiazole or thiaziazole which may be condensed with benzene or each other,

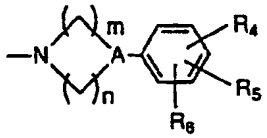
a substituent represented by $-NR_2R_3$ wherein $R_2$ and $R_3$ concurrently or independently represent a hydrogen atom, an alkyl, substituted alkyl or substituted alkenyl group, or a group having the general formula (III):



... (III)

wherein A, $R_4$, $R_5$, $R_6$, a, m and n have the same meanings as defined above,

a substituent represented by the following general formula (IV):



... (IV)

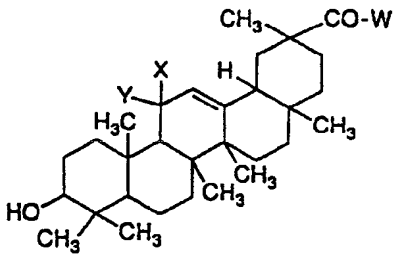
wherein A, $R_4$, $R_5$, $R_6$, m and n have the same meanings as defined above, or

a substituent represented by the following general formula $-NH-(CH_2)a-A_3-R_7$ wherein a has the same meanings as defined above, $A_3$ denotes S, O or NH, and $R_7$ indicates an alkyl, alkenyl, phenyl or substituted phenyl group; the substituents in alkyl, alkenyl or phenyl for $R_2$, $R_3$ and $R_7$ can be as defined above for $R_4$ to $R_6$ (optionally substituted).

The alkyl, alkenyl, alkoxy, etc. substituents may have up to 10 carbon atoms, more preferably up to 5 or 6.

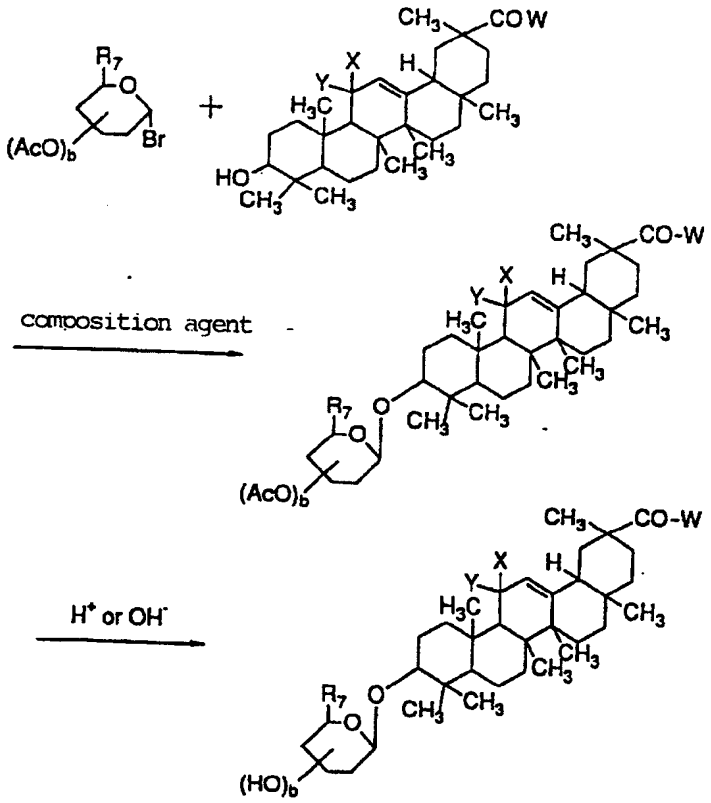
The glycyrrhetinic acid derivatives of the General Formula (I) may be obtained in the form of glycosides by glycosidating a glycyrrhetinic acid derivative that is a compound itself known (as from Japanese Patent Laid-Open Publication No. 63-135351) in the art and represented by the following general formula (V):

General Formula (V)



wherein X, Y and W have the same meanings as defined above, using a glycosyl bromide as a saccharide donor according to conventional synthesis methods. For glycosidating to obtain the glycosides of glycyrrhetinic acid, for instance, the following Koenigs-Knorr type condensation may be used.

Koenigs-Knorr's Condensation Scheme




Here X, Y and W have the same meanings as defined above, $R_7$ stands for a carboxyl or hydroxymethyl group, and b is any desired integer.

The saccharide donors used in this invention, for example, include glycosyl bromides of mono- , di-, oligo- and poly-saccharides or their derivatives. The glycosyl bromides of the monosaccharides, for instance, include those of glucose, fructose, mannose and ribose, of deoxymonosaccharides such as deoxyribose, of amino-saccharides such as glucosamine and mannosamine or of syalic or gluculonic acid. The glucosyl bromides of the disaccharides, for instance, include those of cane sugar, glucuronylglucuronic acid and syalylglucose. The glycosyl bromides of cyclodextrin, oligosaccharides and polysaccharides may be used as well.

By sulfation or phosphation of the thus produced glycosides of the glycyrrhetinic acid derivatives in conventional manners, it may also be possible to obtain the sulfated or phosphated products thereof.

The glycyrrhetinic acid derivatives represented by General Formula (I) according to this invention have strong antiviral action and low toxicity, and may be provided in the form of various pharmaceutical formulations for systemic therapy. The glycyrrhetinic acid derivatives represented by General Formula (I) have a surface active action in themselves, and so may produce good effects by themselves, when topically applied to the site of infection. However, their effects can be more enhanced in combination with absorption enhancers.

Set out below are preferred examples of the novel compounds of this invention which provide efficacious antiviral agents.

(a) 1-(3β-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl) piperazine

(b) 1-(3β-(β-D-glucopyranosyloxy)-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine
(c) 1-(3β-(β-D-glucopyranosyloxy)-11-oxo-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine
(d) 1-(3β-(β-D-glucopyranosyloxy)-18β-olean-12-en-30-oyl)-4-(2-chlorophenyl)piperazine
(e) 1-(3β-(β-D-glucopyranosyloxy)-11-oxo-18β-olean-12-en-30-oyl)-4-(2-chlorophenyl)piperazine
(f) 1-(3β-(β-D-glucopyranosyloxy)-18β-olean-12-en-30-oyl)-4-(2-trifluoromethylphenyl)piperazine
(g) 1-(3β-(β-D-glucopyranosyloxy)-11-oxo-18β-olean-12-en-30-oyl)-4-(2-trifluoromethylphenyl)piperazine
(h) 1-(3β-(β-D-glucopyranosyloxy)-18β-olean-12-en-30-oyl)-4-(2,6-dichlorophenyl)piperazine
(i) 1-(3β-(β-D-glucopyranosyloxy)-11-oxo-18β-olean-12-en-30-oyl)-4-(2,6-dichlorophenyl)piperazine
(j) 3β-(β-D-glucopyranosyloxy)-N-(2-(4-(2-methoxyphenyl)piperazine-1-yl)ethyl)-18β-olean-12-en-30-amide
(k) 3β-(β-D-glucopyranosyloxy)-N-(2-(4-(2-methoxyphenyl)piperazine-1-yl)ethyl)-11-oxo-18β-olean-12-en-30-amide
(l) 3β-(β-D-glucopyranosyloxy)-N-(2-(4-(2-chlorophenyl)piperazine-1-yl)ethyl)-18β-olean-12-en-30-amide
(m) 3β-(β-D-glucopyranosyloxy)-N-(2-(4-(2-chlorophenyl)piperazine-1-yl)ethyl)-11-oxo-18β-olean-12-en-30-amide
(n) 30-((4-(2-methoxyphenyl)piperazine-1-y )carbonyl)-8tβ-olean-12-en-3β-yl-2-O-β-D-glucuronyl-α-D-glucuronic acid
(o) 3β-O-(2,4,6-tri-O-sulfonate)-β-D-glucopyrasyl-11-oxo-18β-olean-12-en-30-oic acid

Salts of Compounds (a)-(n) are useful as well. Particularly efficacious compounds which have been found to have antiviral action are enumerated in Table 1 just below.

Table 1

(1) 1-(3β-acetoxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl) piperazine, m.p.: 210-212°C; MS spectrum: (ED/DI)m/z:672($M^+$, base peak).
(2) 1-(3β-acetoxy-18β-olean-12-en-30-oyl)-4-(3,7,11-trimethyl-2,6,10-dodecatrien-1-yl)piperazine, m.p.: powders; MS spectrum: (ED/DI)m/z:770($M^+$), 69(base peak).
(3) 1-(3β-acetoxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine, m.p.: powders; MS spectrum: (ED/DI) m/z:686($M^+$), 149(base peak).
(4) N-[2-(3,7,11-trimethyl-2,6,10-dodecatrien-1-ylthio)ethyl]-3β-acetoxy-18β-olean-12-en-30-amide, m.p.: 80-85°C, MS spectrum: (ED/DI) m/z: 775($M^+$), 572(base peak).
(5) 1-[3β-(3-carboxy-cis-propenoyloxy)-18β-olean-12-en-30-oyl]-4-(2-methoxyphenyl)piperazine. m.p.:191-193°C, MS spectrum: (EI/DI)m/Z:728($M^+$)
(6) 1-(3β-hydroxy-18β-olean-12-en-30-oyl)-4-(3,7,11-trimethyl-2,6,10-dodecatrien-1-yl)piperazine, m.p.: 102-105°C, MS spectrum: (ED/DI)m/z: 728($M^+$, base peak).
(7) 1-(3β-hydroxy-11-oxo-18β-olean-12-en-30-oyl)-4-(3,7,11-trimethyl-2,6,10-dodecatrien-1-yl)piperazine, m.p.: 179-182°C, MS spectrum: (ED/DI)m/z: 644($M^+$), 149(base peak).
(8) N-[2-(3,7,11-trimethyl-2,6,10-dodecatrien-1-ylthio)ethyl]-3β-acetoxy-11-oxo-18β-olean-12-en-30-amide, m.p.: 80-85°C, MS spectrum: (ED/DI)m/z: 775($M^+$), 572(base peak).
(9) 1-(3β-hydroxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl) piperazine, m.p.: 219-220°C, MS spectrum: (ED/DI)m/z: 630($M^+$), 611(base peak).
(10) 1-[3β-carboxy-cis-propenoyloxy)-18β-olean-12-en-30-oyl]-4-(3,7,11-trimethyl-2,6,10-dodecatrien-1-yl)piperazine, m.p.: 136-138°C, MS spectrum: (ED/DI)m/z: 729($M^+$-97), 69(base peak). (11) 1-[3β-(3-carboxy-cis-propenoyloxy)-11-oxo-18β-olean-12-en-30-oyl]-4-(2-methoxyphenyl)piperazine, m.p.: 168-171°C, MS spectrum: (ED/DI)m/z: 742($M^+$), 149(base peak).
(12) N-[2-(3,3,11-trimethyl-2,6,10-dodecatrien-1-ylthio)ethyl]-3β-(3-carboxy-cis-propenoyloxy)-11-oxo-18β-olean-12-en-30-amide, m.p.: 75-80°C, MS spectrum: (ED/DI)m/z: 734($M^+$-98), 69(base peak).
(13) 1-[3β-(3-carboxypropanoyloxy)-18β-olean-12-en-30-oyl]-4-(2-methoxyphenyl)piperazine, m.p.: 198-200°C, MS spectrum: (ED/DI)m/z: 730($N^1$), 612(base peak).
(14) methyl 3β-(2-carboxyethoxymethoxy)-18β-olean-12-en-30-oate, m.p.: 155-156°C, MS spectrum: (ED/DI)m/z: 556($M^+$), 262(base peak).
(15) disodium-3β-carboxymethoxy-18β-olean-12-en-30-oate, m.p.: 310-312°C (dec.).
(16) 3β-carboxymethoxy-18β-olean-12-en-30-oic acid, MS spectrum: (ED/DI)m/z: 514($M^1$), 248(base peak).
(17) 3β-(2-carbamoylethoxy)-18β-olean-12-en-30-oic acid, m.p.: 290-291°C (dec.), MS spectrum: (ED/DI)m/Z: 527($M^+$), 248(base peak).
(18) disodium-3β-(2-carboxyethoxy)-18β-olean-12-en-30-oate, m.p. 295-300°C (dec.).

The compounds of this invention may be orally administered to patients with viral diseases in liquid, tablet, capsule, (fine) granule, buccal tablet, troche and other forms, which may be prepared according to conventional manners. If desired, they may be used in combination with absorption enhancers such as surface active agents,

e.g. bile salts or saponins or polyoxyethylene higher alcohol ethers. Although varying depending upon the type of the compounds, the conditions of patients and the form of the preparations, they may generally be administered to adult patients in doses in the range of 10 to 5000 mg a day.

The compounds of this invention may be formulated into conventional injectable forms. In this case, they may generally be administered to human patients in doses of 30 to 3000 mg a day, although depending upon the type of compound and the conditions of the patients.

For topical therapy, the compounds of this invention may be formulated into conventional liquid, ointment, cream, hydrogel or suppository (for both the rectum and vagina) forms, and may be prepared as an eye lotion and ointment. These compositions may contain absorption enhancers such as surface active agents, e.g. bile salts, saponins and polyoxyethylene higher alcohol ethers, polethylene glycol, DMSO and laurocaplam. Although varying with the type of the compounds, the conditions of human patients, the form of preparations, etc., these drugs may contain the compounds in amounts of 0.01 to 10%.

## EXAMPLES

The present invention will now be explained more specifically but not exclusively with reference to examples of compound production, pharmacological tests and pharmaceutical compositions.

### Example 1

1-(3β-acetoxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl;-piperazine (1a)

To a solution of 3β-acetoxy-18β-olean-12-en-30-oyl chloride (15.0 g, 29.1 mmol) and triethylamine (2.94 g, 29.1 mmol) in dichloromethane (200 ml), 1-(2-methoxyphenyl) piperazine (5.59 g, 29.1 mmol) was added, followed by stirring for 2 hours at 10-20°C.

The reaction mixture was washed with water, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (dichloromethane) to obtain 19.3 g (98.6%) of the desired compound having the following physical properties.

Melting Point: 210-212°C, and Mass Spectrum (EI/DI)m/z: 672 ($M^+$, base peak).

### Example 2

1-(3β-acetoxy-18β-olean-12-en-30-oyl)-4-(2-chlorophenyl)-piperazine (1b)

This compound was prepared by following the procedure of Example 1 with the exception that 1-(2-chlorophenyl)piperazine was used instead of 1-(2-methoxylphenyl)piperazine.

Mass Spectrum (EI/DI)m/z: 676 ($M^+$), 189 (base peak)

### Example 3

1-(3β-acetoxy-18β-olean-12-en-30-oyl)-4-(2-trifluoromethylphenyl)piperazine (1c)

This compound was prepared by following the procedure of Example 1 with the exception that 1-(2-trifluoromethylphenyl)piperazine was used instead of 1-(2-methoxyphenyl)piperazine.

Mass Spectrum (EI/DI)m/z: 710 ($M^+$, base peak)

### Example 4

1-(3β-acetoxy-18β-olean-12-en-30-oyl)-4-(2,6-dichlorophenyl)piperazine (1d)

This compound was prepared by following the procedure of Example 1 with the exception that 1-(2,6-dichlorophenyl)piperazine was used instead of 1-(2-methoxyphenyl)piperazine.

Mass Spectrum (EI/DI)m/z: 710($M^+$, base peak)

### Example 5

3β-acetoxy-N-(2-4-(2-methoxyphenyl)piperazine-1-yl)ethyl)-18β-olean-12-en-30-amide (1e)

This compound was prepared by following the procedure of Example 1 with the exception that 1-(2-aminoethyl)-4-(2-methoxyphenyl) piperazine was used instead of 1-(2-methoxyphenyl)piperazine.

Mass Spectrum (EI/DI)m/z: 715($M^+$), 205(base peak)

Example 6

3β-acetoxy-N-(2-4-(2-chlorophenyl)piperazine-1-yl)ethyl)-18β-olean-12-en-30-amide (1f)

This compound was prepared by following the procedure of Example 1 with the exception that 1-(2-aminoethyl)-4-(2-methoxyphenyl)piperazine was used instead of 1-(2-methoxyphenyl)piperazine.

Mass Spectrum (EI/DI)m/z: 719($M^+$), 205(base peak)

Example 7

1-(3β-acetoxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (2a)

To a solution of 3β-acetoxy-11-oxo-18β-olean-12-en-30-oyl chloride (26.6g, 50.0 mmol) and triethylamine (5.06 g, 550.0 mmol) in dichloromethane (400 ml), 1-(2-methoxyphenyl -piperazine (9.60 g, 50.0 mmol) was added, followed by stirring for 2 hours at 10-20°C.

The reaction mixture was washed with water, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (dichloromethane) to give 34.4 g (100%) of the desired compound in the form of colorless powders.

Mass spectrum (EI/DI)m/z: 686 ($M^+$, base peak).

Example 8

1-(3β-acetoxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2-chlorophenyl)piperazine (2b)

This compound was prepared by following the procedure of Example 7 with the exception that 1-(2-trifluoromethylphenyl)piperazine was used instead of 1-(2-methoxyphenyl)piperazine.

Mass spectrum (EI/DI)m/z: 690 ($M^+$, base peak).

Example 9

1-(3β-acetoxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2-trifluoromethylphenyl)piperazine (2c)

This compound was prepared by following the procedure of Example 7 with the exception that 1-(2-trifluoromethylphenyl) piperazine was used instead of 1-(2-methoxyphenyl)piperazine.

Mass spectrum (EI/DI)m/z: 724 ($M^+$, base peak).

Example 10

1-(3β-acetoxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2,6-dichlorophenyl)piperazine (2d)

This compound was prepared by following the procedure of Example 7 with the exception that 1-(2,6-dichrolophenyl)piperazine was used instead of 1-(2-methoxyphenyl)piperazine.

Mass spectrum (EI/DI)m/z: 724 ($M^+$, base peak).

Example 11

3β-acetoxy-N-(2-4-(2-methoxyphenyl)piperazine-1-yl)ethyl)-11-oxo-18β-olean-12-en-30-amide(2e)

This compound was prepared by following the procedure of Example 7 with the exception that 1-(2-aminoethyl)-4-(2-methoxyphenyl) piperazine was used instead of 1-(2-methoxyphenyl)piperazine.

Mass spectrum (EI/DI)m/z: 729 ($M^+$,) 205(base peak).

Example 12

3β-acetoxy-N-(2-4-(2-chlorophenyl)piperazine-1-yl)ethyl)-11-oxo-18β-olean-12-en-30-amide(2f)

This compound was prepared by following the procedure of Example 7 with the exception that 1-(2-aminoethyl)-4-(2-chlorophenyl) piperazine was used instead of 1-(2-methoxyphenyl)piperazine.

Mass Spectrum (EI/DI) m/z: 733 ($M^+$, base peak).

Example 13

1-(3β-hydroxy-18β-olean-12-en-30-oyl-4-(2-methoxyphenyl) piperazine(3a)

To a solution of 1-(3β-acetoxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine(1a)(17.5g,26.0 mmol, obtained in Example 1) in 1,4-dioxane(100ml),20% NaOH/methanol(100ml) was added, followed by stirring for 5 hours at 20°C.

The reaction mixture was poured into ice water and then extracted with chloroform (150mlx2). The resulting organic layer was collected, washed with a saturated NaCl solution, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (5% diethyl ether/dichloromethane) to give 13.3g(81.0%) of the desired compound having the following physical data.
Melting point: 219-220°C.
Mass spectrum (EI/DI)m/z: 630 ($M^+$),149(base peak).

Example 14

1-(3β-hydroxy-18β-olean-12-en-30-oyl)-4-(2-chlorophenyl)piperazine (3b)

This compound was prepared by following the procedure of Example 13 with the exception that 1-(3β-acetoxy-18β-olean-12-en-30-oyl)-4-(2-chlorophenyl)piperazine(1b)(obtained in Example 2) was used instead of 1-(3β-acetoxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl))piperazine (1a).
Mass Spectrum (EI/DI)m/z: 634 ($M^+$), 189(base peak).

Example 15

1-(3β-hydroxy-18β-olean-12-en-30-oyl)-4-(2-trifluoromethylphenyl)piperazine (3c)

This compound was prepared by following the procedure of Example 13 with .the exception that 1-(3β-acetoxy-18β-olean-12-en-30-oyl)-4-(2-trifluoromethylphenyl)piperazine(1c)(obtained in Example 3) was used instead of 1-(3β-acetoxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (1a).
Mass spectrum (EI/DI)m/z: 668 ($M^+$),189(base peak).

Example 16

1-(3β-hydroxy-18β-olean-12-en-30-oyl)-4-(2,6-dichlorophenyl)piperazine (3d)

This compound was prepared by following the procedure of Example 13 with the exception that 1-(3β-acetoxy-18β-olean-12-en-30-oyl)-4-(2,6-dichlorophenyl)piperazine(1d)(obtained in Example 4) was used instead of 1-(3β-acetoxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (1a).
Mass spectrum (EI/DI)m/z: 668 ($M^+$,base peak).

Example 17

3β-hydroxy-N-(2-4-(2-methoxyphenyl)piperazine-1-yl)ethyl)-18β-olean-12-en-30-amide(3e)

This compound was prepared by following the procedure of Example 13 with the exception that 3β-acetoxy-N-(2-4-(2-methoxyphenyl)piperazine-1-yl)ethyl-18β-olean-12-en-30-amide(1e)(obtained in Example 5) was used instead of 1-(3β-acetoxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (1a).
Mass spectrum (EI/DI)m/z: 673 ($M^+$),205(,base peak).

Example 18

3β-hydroxy-N-(2-4-(2-chlorophenyl)piperazine-1-yl)ethyl)-18β-olean-12-en-30-amide (3f)

This compound was prepared by following the procedure of Example 13 with the exception that 3β-acetoxy-N-(2-4-(2-chlorophenyl)piperazine-1-yl)ethyl-18β-olean-12-en-30-amide (1f) (obtained in Example 6) was used instead of 1-(3β-acetoxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (1a).
Mass Spectrum (EI/DI)m/z: 677($M^+$), 209(base peak).

Example 19

1-(3β-hydroxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (4a)

To a solution of 1-(3β-acetoxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (2a) (31.8 g, 46.4 mmol, obtained in Example 7) in 1,4-dioxane (360 ml), 5% NaOH/methanol (360 ml) was added, followed by stirring for 3 hours at 20°C.

The reaction mixture was poured into ice water and then extracted with chloroform (500 ml x 2). The organic layer was collected, washed with a saturated NaCl solution dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (5% diethyl ether/dichloromethane) to give 22.9 g (76.6%) of the desired compound having the following physical data.
Melting Point: 179-182°C; Mass Spectrum (EI/DI)m/z: 644($M^+$), 149(base peak).

Example 20

1-(3β-hydroxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2-chlorophenyl)piperazine (4b)

This compound was prepared by following the procedure of Example 19 with the exception that 1-(3β-acetoxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2-chlorophenyl)piperazine (2b) obtained in Example 8) was used instead of 1-(3β-acetoxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (2a).
Mass Spectrum (EI/DI)m/z: 648($M^+$, base peak).

Example 21

1-(3β-hydroxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2-trifluoromethylphenyl)piperazine(4c)

This compound was prepared by following the procedure of Example 19 with the exception that 1-(3β-acetoxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2-trifluoromethylphenyl)piperazine (2c) (obtained in Example 9) was used instead of 1-(3β-acetoxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (2a).
Mass Spectrum (EI/DI)m/z: 682($M^+$, base peak).

Example 22

1-(3β-hydroxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2,6-dichlorophenyl)piperazine (4d)

This compound was prepared by following the procedure of Example 19 with the exception that 1-(3β-acetoxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2,6-dichlorophenyl)piperazine (2d) (obtained in Example 10) was used instead of 1-(3β-acetoxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (2a).
Mass Spectrum (EI/DI)m/z: 682($M^+$, base peak).

Example 23

3β-hydroxy-N-(2-4-(2-methoxyphenyl)piperazine-1-yl)ethyl)-11-oxo -18β-olean-12-en-30-amide (4e)

This compound was prepared by following the procedure of Example 19 with the exception that 3β-acetoxy-N-(2-4-(2-methoxyphenyl )piperazine-1-yl)ethyl-11-oxo-18β-olean-12-en-30-amide (2e) (obtained in Example 11) was used instead of 1-(3β-acetoxy -11-oxo-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (2a).
Mass Spectrum (EI/DI)m/z: 687($M^+$), 205(base peak).

Example 24

3β-hydroxy-N-(2-4-(2-chlorophenyl)piperazine-1-yl)ethyl)-11-oxo-18β-olean-12-en-30-amide (4f)

This compound was prepared by following the procedure of Example 19 with the exception that 3β-acetoxy-N-(2-4-(2-chlorophenyl)piperazine-1-yl)ethyl-11-oxo-18β-olean-12-en-30-amide (2f) (obtained in Example 12) was used instead of 1-(3β-acetoxy -11-oxo-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (2a).
Mass Spectrum (EI/DI)m/z: 691($M^+$, base peak).

Example 25

1-(3β-(β-D-glucopyranosyloxy)-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (5a)

A mixture of 1-(3β-hydroxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (3a) (4.00g, 6.34mmol, obtained in Example 13), drierite (16.0g,0.118mmol),iodine (0.800g, 6.30mmol),$Ag_2O$ (14.7g, 63.4mmol), and absolute chloroform (80ml) was stirred for 30 minutes at 20°C. Then, to the mixture, a solution of tetra-O-acetyl-α-D-glucopyranosyl bromide in absolute chloroform (80ml) was added over 10 minutes, followed by stirring for 24 hours at 20°C.

The reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (5% diethyl ether/dichloromethane) to give 5.28g (91.2%) of 1-(3β-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranoxyloxy)-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine(5'a) having the following physical data.

The obtained 5'a was dissolved in a mixture of chloroform and methanol (3:1), and to the mixture 0.1M sodium methoxide (300ml, 30mmol) was added, followed by stirring for 15 hours at 20°C. The reaction mixture was regulated to pH5-6 with 5% HCl and concentrated in vacuo. The residue was extracted with chloroform (400ml) and water (400ml). The organic layer were collected, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (chloroform:diethyl ether=10:1-chloroform:methanol=20:1) to give 4.34g(86.3%) of the desired compound having the following physical data,

as colorless powders.
(5'a)
$^1$H-NMR spectrum ($CDCl_3$)δppm:
0.80,0.87,0.88,0.96,1.13,1.23(21H,sx6,$CH_3$x7),1.2-2.2(23H,m,CH and $CH_2$),2.01,2.02,2.20(12H,sx6,$CH_3$COx4), 3.05(4H,brs,$CH_2$x2), 3.15(1H,brs,$C_3$-H),3.2-3.7(3H,m,$C'_5$-H and $C'_6$-H),3.7-3.9(4H,m,$CH_2$x2),3.88(3H,s,$OCH_3$), 4.34(2H,brs,$C'_2$-H and $C'_4$-H),4.92(1H,brs,$C'_1$-H),5.21(1H,brs,$C'_3$-H),5.3-5.4(1H,m,$C_{12}$-H),6.9-7.4(4H,m,aromatic H)
(5a)
$^1$H-NMR spectrum ($CDCl_3$)δppm:
0.80,0.87,0.88,0.96,1.13,1.23(21H,sx6,$CH_3$x7),1.2-2.2(23H,m,CH and $CH_2$),3.05(4H,brs,$CH_2$x2),3.15(1H,brs,$C_3$-H), 3.2-3.7(3H,m,$C'_5$-H and $C'_6$-H),3.7-3.9(4H,m,$CH_2$x2),3.88(3H,s,$OCH_3$), 4.34(2H,brs, $C'_2$-H and $C'_4$-H), 4.92(1H,brs,$C'_1$-H),5.21(1H,brs,$C'_3$-H),5.3-5.4(1H,m,$C_{12}$-H),6.9-7.4(4H,m,aromatic H)

Example 26

1-(3β-(β-D-glucopyranosyloxy)-18β-olean-12-en-30-oyl)-4-(2-chlorophenyl)piperazine (5b)
This compound was prepared by following the procedure of Example 25 with the exception that 1-(3β-hydroxy-18β-olean-12-en-30-oyl)-4-(2-chlorophenyl)piperazine(3b)(obtained in Example 14) was used instead of 1-(3β-hydroxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine(3a).
$^1$H-NMR spectrum ($CDCl_3$) δppm:
0.79,0.81,0.94,0.96,1.00,1.14,1.23(21H,sx7,$CH_3$x7),0.8-2.1(23H,m,CH and $CH_2$),3.03(4H,brs,$CH_2$x2), 3.15(1H,brs,$C_3$-H), 3.2-3.7(3H,m,$C'_5$-H and $C'_6$-H),3.7-3.9(4H,m,$CH_2$x2),4.34(2H,brs,$C'_2$-H and $C'_4$-H),4.92(1H,brs,$C'_1$-H), 5.21(1H,brs,$C'_3$-H),5.3-5.4(1H,m,$C_{12}$-H),7.0-7.4(4H,m,aromatic H)

Example 27

1-(3β-(β-D-glucopyranosyloxy)-18β-olean-12-en-30-oyl)-4-(2-trifluoromethylphenyl)piperazine(5c)
This compound was prepared by following the procedure of Example 25 with the exception that 1-(3β-hydroxy-18β-olean-12-en-30-oyl)-4-(2-trifluoromethylphenyl)piperazine(3c)(obtained in Example 15) was used instead of 1-(3β-hydroxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine(3a).
$^1$H-NMR spectrum ($CDCl_3$) δppm:
0.79,0.82,0.95,0.97,1.00,1.14,1.23(21H,sx7,$CH_3$x7),0.7-2.1(23H,m,CH and $CH_2$),2,8-3.0(4H,brs,$CH_2$x2),3.20(1H,brs, $C_3$-H),3.2-3.7(3H,m,$C'_5$-H and $C'_6$-H),3.7-3.9(4H,m,$CH_2$x2), 4.34(2H,brs,$C'_2$-H and $C'_4$-H),4.92(1H,brs,$C'_1$-H),5.21(1H,brs, $C'_3$-H),5.3-5.4(1H,m,$C_{12}$-H),7.2-7.6(4H,m,aromatic H)

Example 28

1-(3β-(β-D-glucopyranosyloxy)-18β-olean-12-en-30-oyl)-4-(2,6-dichlorophenyl)piperazine(5d)
This compound was prepared by following the procedure of Example 25 with the exception that 1-(3β-hydroxy-18β-olean-12-en-30-oyl)-4-(2,6-dichlorophenyl)piperazine(3d)(obtained in Example 16) was used instead of 1-(3β-hydroxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine(3a).
$^1$H-NMR spectrum ($CDCl_3$) δppm:
0.79,0.81,0.94,0.96,1.00,1.14,1.23(21H,sx7,$CH_3$x7),0.8-2.1(23H,m,CH and $CH_2$),3.03(4H,brs,$CH_2$x2),3.15(1H,brs, $C_3$-H),3.2-3.7(3H,m,$C'_5$-H and $C'_6$-H),3.7-3.9(4H,m,$CH_2$x2), 4.34(2H,brs,$C'_2$-H and $C'_4$-H),4.92(1H,brs,$C'_1$-H),5.21(1H,brs, $C'_3$-H),5.3-5.4(1H,m,$C_{12}$-H),7.2-7.4(3H,m,aromatic H)

Example 29

3β-(β-D-glucopyranosyloxy)-N-(2-4-(2-methoxyphenyl)piperazine-1-yl)ethyl-18β-olean-12-en-30-amide (5e)
This compound was prepared by following the procedure of Example 25 with the exception that 3β-hydroxy-N-(2-4-(2-methoxyphenyl)piperazine-1-yl)ethyl-18β-olean-12-en-30-amide (3e)(obtained in Example 17) was used instead of 1-(3β-hydroxy -18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine(3a).
$^1$H-NMR spectrum ($CDCl_3$) δppm:
0.79,0.91,0.95,1.00,1.11,1.15(21H,sx6,$CH_3$x7),0.7-2.1(23H,m,CH and $CH_2$),2.5-2.6(2H,m,$CH_2$),2.6-2.8(4H,m,piperazine), 3.15(1H,m,$C_3$-H),3.0-3.2(4H,m,piperazine),3.2-3.7(3H,m,$C'_5$-H and $C'_6$-H),3.3-3.5(2H,m,$CH_2$),3.87(3H,s,$OCH_3$), 4.34(2H,brs,$C'_2$-H and $C'_4$-H),4.92(1H,brs,$C'_1$-H),5.21(1H,brs,$C'_3$-H),5.41(1H,m,$C_{12}$-H),6.45(1H,brs,CONH), 6.8-7.1(4H,m,aromatic H)

Example 30

3β-(β-D-glucopyranosyloxy)-N-(2-4-(2-chlorophenyl)piperazine-1-yl)ethyl-18β-olean-12-en-30-amide (5f)

This compound was prepared by following the procedure of Example 25 with the exception that 3β-hydroxy-N-(2-4-(2-chlorophenyl)piperazine-1-yl)ethyl-18β-olean-12-en-30-amide (3f)(obtained in Example 18) was used instead of 1-(3β-hydroxy -18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine(3a).

$^1$H-NMR spectrum $CDCl_3$) δppm:

0.79,0.82,0.94,0.97,1.00,1.14,1.22(21H,sx7,$CH_3$x7),0.8-2.1(23H,m,CH and $CH_2$),2.5-2.6(2H,m,$CH_2$),2.6-2.8(4H,m, piperazine),3.15(1H,m,$C_3$-H),3.0-3.2(4H,m,piperazine),3.2-3.7(3H,m,C′$_5$-H and C′$_6$-H),3.3-3.5(2H,m,$CH_2$), 4.34(2H,brs,C′$_2$-H and C′$_4$-H),4.92(1H,brs,C′$_1$-H),5.21(1H,brs,C′$_3$-H),5.33(1H,m,$C_{12}$-H),6.45(1H,brs,CONH),7.0-7.4(4H,m,aromatic H)

Example 31

1-(3β-(β-D-glucopyranosyloxy)-11-oxo-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (6a)

This compound was prepared by following the procedure of Example 25 with the exception that 1-(3β-hydroxy-11-oxo-18β-olean -12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (4a)(obtained in Example 19) was used instead of 1-(3β-hydroxy-18β -olean-12-en-30-oyl)-4-(2-methoxyphenyl) piperazine (3a).

$^1$H-NMR spectrum ($CDCl_3$) δppm:

0.82,0.89,0.91,0.98,1.15,1.26(21H,sx6,$CH_3$x7),1.2-2.2(21H,m,CH and $CH_2$),2.9-3.1(4H,brs,$CH_2$x2),3.16(1H,brs, $C_3$-H),3.2-3.7 (3H,m,C′$_5$-H and C′$_6$-H),3.7-3.9(4H,m,$CH_2$x2), 3.88(3H,s, $OCH_3$), 4.34(2H,brs,C′$_2$-H and C′$_4$-H),4.92(1H,brs,C′$_1$-H), 5.21(1H,brs, C′$_3$-H),5.7-5.8(1H,m,$C_{12}$-H),7.0-7.5(4H,m,aromatic H)

Example 32

1-(3β-(β-D-glucopyranosyloxy)-11-oxo-18β-olean-12-en-30-oyl)-4-(2-chlorophenyl)piperazine (6b)

This compound was prepared by following the procedure of Example 25 with the exception that 1-(3β-hydroxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2-chlorophenyl)piperazine(4b)(obtained in Example 20) was used instead of 1-(3β-hydroxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine (3a).

$^1$H-NMR spectrum ($CDCl_3$) δppm:

0.81,0.83,0.97,0.99,1.02,1.16,1.25(21H,sx7,$CH_3$x7),0.8-2.1(21H,m,CH and $CH_2$),2.9-3.1(4H,m,$CH_2$x2),3.15(1H,brs, $C_3$-H),3.2-3.7 (3H,m,C′$_5$-H and C′$_6$-H),3.7-3.9(4H,m,$CH_2$x2), 4.34(2H,brs,C′$_2$-H and C′$_4$-H),4.92(1H,brs,C′$_1$-H), 5.21(1H,brs, C′$_3$-H),5.7-5.8(1H,m,$C_{12}$-H),7.1-7.5(4H,m,aromatic H)

Example 33

1-(3β-(β-D-glucopyranosyloxy)-11-oxo-18β-olean-12-en-30-oyl)-4-(2-trifluoromethylphenyl)piperazine(6c)

This compound was prepared by following the procedure of Example 25 with the exception that 1-(3β-hydroxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2-trifluoromethylphenyl) piperazine(4c)(obtained in Example 21) was used instead of 1-(3β-hydroxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine(3a).

$^1$H-NMR spectrum ($CDCl_3$) δppm:

0.81,0.84,0.97,0.99,1.02,1.16,1.25(21H,sx7,$CH_3$x7),0.7-2.1(21H,m,CH and $CH_2$),2.8-3.0(4H,m,$CH_2$x2),3.20(1H,brs, $C_3$-H),3.2-3.7 (3H,m,C′$_5$-H and C′$_6$-H),3.7-3.9(4H,m,$CH_2$x2), 4.34(2H,brs,C′$_2$-H and C′$_4$-H),4.92(1H,brs,C′$_1$-H), 5.21(1H,brs, C′$_3$-H),5.7-5.8(1H,m,$C_{12}$-H),7.3-7.7(4H,m,aromatic H)

Example 34

1-(3β-(β-D-glucopyranosyloxy)-11-oxo-18β-olean-12-en-30-oyl)-4-(2,6-dichlorophenyl)piperazine (6c)

This compound was prepared by following the procedure of Example 25 with the exception that 1-(3β-hydroxy-11-oxo-18β-olean-12-en-30-oyl)-4-(2,6-dichlorophenyl) piperazine (4c)(obtained in Example 22) was used instead of 1-(3β-hydroxy-18β -olean-12-en-30-oyl)-4-(2-methoxyphenyl) piperazine(3a).

$^1$H-NMR spectrum ($CDCl_3$) δppm:

0.81,0.83,0.96,0.99,1.02,1.16,1.25(21H,sx7,$CH_3$x7),0.8-2.1(21H,m,CH and $CH_2$),2.8-3.0(4H,m,$CH_2$x2),3.15(1H, brs,$C_3$-H),3.2-3.7(3H,m,C′$_5$-H and C′$_6$-H),3.7-3.9(4H,m,$CH_2$x2), 4.34(2H,brs,C′$_2$-H and C′$_4$-H),4.92(1H,brs,C′$_1$-H), 5.21(1H,brs, C′$_3$-H),5.7-5.8(1H,m,$C_{12}$-H),7.3-7.5(3H,m,aromatic H).

Example 35

3β-(β-D-glucopyranosyloxy)-N-(2-4-(2-methoxyphenyl)piperazine-1-yl)ethyl)-11-oxo-18β-olean-12-en-30-amide (6e)

This compound was prepared by following the procedure of Example 25 with the exception that 3β-hydroxy-N-(2-4-(2-methoxyphenyl)piperazine-1-yl)ethyl)-11-oxo-18β-olean-12-en-30-amide (3e) (obtained in Example 23) was used instead of 1-(3β-hydroxy -18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl) piperazine (3a).

$^1$H-NMR spectrum ($CDCl_3$) δppm:

0.81,0.93,0.97,1.02,1.13,1.17(21H,sx6,$CH_3$x7),0.7-2.1(21H,m,CH and $CH_2$),2.5-2.6(2H,m,$CH_2$), 2.6-2.8(4H, m, piperazine), 3.15 (1H, m, $C_3$-H) and C′$_6$-H), 3.0-3.2(4H, m, piperazine), 3.2-3.7(3H, m, C′$_5$-H and C′$_6$-H), 3.3-3.5(2H, m, $CH_2$), 3.87(3H, s, $OCH_3$), 4.34(2H, brs, C′$_2$-H and C′$_4$-H), 4.92(1H, brs, C′$_1$-H), 5.21(1H, brs, C′$_3$-H), 5.7-5.8(1H, m, $C_{12}$-H, 6.45(1H, brs, CONH), 6.9-7.2(4H, m, aromatic H).

Example 36

3β-(β-D-glucopyranosyloxy)-N-(2-4-(2-chlorophenyl)piperazine-1-yl)ethyl)-11-oxo-18β-olean-12-en-30-amide (6f)

This compound was prepared by following the procedure of Example 25 with the exception that 3β-hydroxy-N-(2-4-(2-chlorophenyl)piperazine-1-yl)ethyl)-11-oxo-18β-olean-12-en-30-amide (3f) (obtained in Example 24) was used instead of 1-(3β-hydroxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl) piperazine (3a).

$^1$H-NMR spectrum ($CDCl_3$) δppm:

0.81, 0.85, 0.96, 0.99, 1.02, 1.16, 1.24(21H, sx7, $CH_3$x7), 0.8-2.1(21H, m, CH an $CH_2$), 2.5-2.6(2H, m, $CH_2$), 2.6-2.8(4H, m, piperazine), 3.15(1H, m, $C_3$-H), 3.0-3.2(4H, m, piperazine), 3.2-3.7(3H, m, C′$_5$-H and C′$_6$-H), 3.3-3.5(2H, m, $CH_2$), 4.34(2H, brs, C′$_2$-H and C′$_4$-H), 4.92(1H, brs, C′$_1$-H), 5.21(1H, brs, C′$_3$-H), 5.7-5.8(1H, m, $C_{12}$-H), 6.45(1H, brs, CONH), 7.0-7.4(4H, m, aromatic H).

Example 37

30-((4-(2-methoxylphenyl)piperazine-1-yl)carbonyl)-18β-olean-12-en-3β-yl-2-O-β-D-glucuronyl-α-D -glucuronic acid(7)

This compound was prepared by following the procedure of Example 25 with the exception that dimethyl-2,3-di-O-acetyl-1-bromo-deoxy-2-O-(2,3,4-tri-O-acetyl-β-D-glucuronyl)-α-D-glucuronic acid diester was used instead of tetra-O-acetyl-α-D-glucopyranosyl bromide.

The precipitate was filtered off, and the filtrate was concentrated in vacuo. The reside was refluxed in a solution of 5% NaOH:ethanol (3:1) for 3 hours, neutralized with Amberlite IR-120 ($H^+$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (chloroform:methanol=20:1) to give 2.64 g (41.6%) of the desired compound in the form of colorless powders.

$^1$H-NMR Spectrum ($CDCl_3$) δppm:

0.81, 0.88, 0.89, 0.97, 1.14, 1.24(21H, sx6, $CH_3$x7), 1.2-2.2(23H, m, CH and $CH_2$), 3.05(4H, brs, $CH_2$x2), 3.35(1H, brs, $C_3$-H), 3.2-3.7(2H, m, C′$_5$-H and C″$_5$-H), 3.7-3.9(4H, m, $CH_2$x2), 3.88(3H, s, $OCH_3$), 4.34(4H, brs, C′$_2$-H, C″$_2$-H, C′$_4$-H and C″$_4$-H), 4.92(2H, brs, C′$_1$-H and C″$_1$-H), 5.21(2H, brs, C′$_3$-H and C″$_3$-H), 5.3-5.4(1H, m, $C_{12}$-H), 6.9-7.4(4H, m, aromatic H).

Example 38

3β-(2,4,6-tri-O-sodiosulfonato-β-D-glucopyranosyloxy)-11-oxo-18β-olean-12-en-30-oic acid (8)

Sulfur trioxide pyridine complex (10.06 g) was added to a solution of 3β-(β-D-glucopyranosyloxy)-11-oxo-18β-olean-12-en-30-oic acid (5.00 g) in DMF (100ml), followed by stirring for 17 hours at 20°C. The reaction mixture was poured into diethyl ether (500 ml), followed by stirring. The precipitated yellow oil was washed with dichloromethane (200 ml), dissolved in ion exchanged water, regulated to pH 5-6 with 1N NaOH, and lyophilized. The residue was purified by silica gel column chromatography to give 6.20 g (81.6%) of the desired compound in the form of colorless powder.

$^1$H-NMR spectrum ($CDCl_3$) δppm:

0.81(3H, s, $CH_3$), 0.86(3H, s, $CH_3$), 1.06(6H, s, $CH_3$x2), 1.13(&H, s, $CH_3$x2), 1.41(sH, s, $CH_3$), 2.50-2.60(1H, m, $C_{18}$-H), 2.55(1H, s, $C_9$-H), 3.30(1H, dd, J=10.74, 5.37Hz, $C_3$-H), 4.16-4.26(2H, m, $C_5$-H, $C_{6b}$-H), 4.39(1H, dd, J=9.28, 6.84Hz, $C_{6a}$-H), 4.49(1H, m, $C_2$-H), 4.61(1H, m, $C_4$-H), 4.82(1H, dd, J=4.88, 3.90Hz, $C_3$-H), 4.91(1H, d. J=5.38Hz, $C_1$-H), 5.70(1H, s, $C_{12}$-H).

Pharmacological Efficacy Testing - 1

Antiviral Action Against Herpes Simplex Virus Type 1 and Cytotoxicity

For incubation, HSV-1 (Miyama strain) and the compounds to be tested were added to monolayers of GMK cells (derived from the kidney of a green monkey) grown on 96-holed culture plates. After incubation, the cytopathic effect (CPE) of the viruses as well as the effect of the compounds on CPE inhibition and on their cytotoxicity were microscopically observed. To estimate the antiviral action of the compounds, $TCID_{50}$ values were found using the CPE as an index and $\Delta TCID_{50}$ ($log_{10}$) values were calculated by the $TCID_{50}$ values of both the compound-treated group and the control group. Bear in mind that prior to be added to the incubation systems, the compounds were regulated with MEM or ethanol media to 10 mg/ml concentrations, and diluted with MEM media containing 1% bovine fetus serum.

Table 2-1

In Vitro Antiviral Action of Compounds on Cells Infected with HSV-1(Miyama Strain)

| Compounds | Antiviral Activity ($\Delta TCID_{50}$ ($log_{50}$)) | | |
|---|---|---|---|
| Comp. Concn. (μg/ml) | 1 | 5 | 25 |
| Comp. Ex. 25 | 1.86(-) | >3.00 (-) | >3.56 (±) |
| Comp. Ex. 37 | 1.94(-) | >3.17 (-) | >3.73 (-) |
| Table 1, Comp. (5) | 1.0 (-) | 2.1 (-) | 3.1 (-) |
| (9) | 1.3 (-) | 1.2 (+) | (++) |
| (10) | 0.7 (-) | 2.0 (+) | 1.9 (+) |
| (13) | 0.8 (-) | 2.6 (-) | 2.5 (+) |
| (15) | 0.0 (-) | 0.3 (-) | 1.0 (+) |
| (18) | 0.7 (-) | 1.6 (-) | 1.2 (+) |
| Carbenoxolone | 0.2 (-) | 0.3 (-) | 2.4 (+) |
| Ara-a | 1.2 (-) | 1.5 (+) | 2.5 (+) |

( ) stands for the magnitude of cytotoxicity [(-): no cytotoxicity, and (±): less cytotoxicity]

Table 2-2

Action of Compounds on HSV (UV-238 Strain)

| Compounds | Antiviral Activity ($\Delta TCID_{50}$ ($log_{50}$)) | | |
|---|---|---|---|
| Comp. Concn. (μg/ml) | 1 | 5 | 25 |
| Table 1, Comp. (5) | 1.3 (-) | 2.2 (-) | 2.8 (-) |
| (9) | 0.7 (-) | 1.3 (+) | 2.5 (+) |
| (13) | 0.9 (-) | 1.4 (-) | 2.5 (+) |
| Carbenoxolone | 0.2 (-) | 0.2 (-) | 2.2 (+) |
| Ara-a | 1.1 (-) | 1.7 (+) | 2.6 (+) |

( ) stands for the magnitude of cytotoxicity [(-): no cytotoxicity, and (±): less cytotoxicity but antiviral activity found]

Pharmacological Efficacy Testing - 2

Antiviral Spectrum

For incubation, HSV-1 (KOS strain), HSV-2 (UW-268 strain), vaccinia viruses (D1E strain) or influenza viruses (A/PR/8 strain) and the compounds to be tested were added to monolayers of cells grown on 96-holed culture plates. After incubation, the cytopathic effect (CPE) of the viruses as well as the effect of the compounds on CPE inhibition and on their cytotoxicity were microscopically observed. To estimate the antiviral action of the compounds, $TCID_{50}$ values were found using the CPE as an index and $\Delta TCID_{50}$ ($log_{10}$) values were calculated by the $TCID_{50}$ values of both the compound-treated group and the control group. MDCK cells were infected with influenza viruses and Vero cells with other viruses. Bear in mind that prior to being added to the incubation system, the compounds were mixed with MEM media to 10 mg/ml concentrations and diluted with MEM medium with 1% bovin fetus serum.

Table 3 - Antiviral Spectrum

| Viruses under Test | Antiviral Activity ($\Delta TCID_{50}$ ($log_{50}$)) | | |
|---|---|---|---|
| Comp. Ex. 25 | | | |
| Comp. Concn. (μg/ml) | 1 | 5 | 25 |
| Herpes Simplex Viruses | | | |
| Type 1 | 2.04 (-) | >3.19 (-) | >3.31 (±) |
| Type 2 | 1.85 (-) | 2.92 (-) | >3.30 (±) |
| Vaccinia Viruses | 1.70 (-) | 2.67 (-) | 2.53 (±) |
| Influenza Viruses | 1.31 (-) | 1.86 (-) | 2.22 (±) |
| Comp. Ex. 37 | | | |
| Comp. Concn. (μg/ml) | 1 | 5 | 25 |
| Herpes Simplex Viruses | | | |
| Type 1 | 2.74 (-) | 2.65 (-) | >3.25 (-) |
| Type 2 | 1.87 (-) | 3.01 (-) | >3.85 (-) |
| Vaccinia Viruses | 1.49 (-) | 2.85 (-) | 2.61 (-) |
| Influenza Viruses | 1.64 (-) | 1.70 (-) | 2.38 (±) |

( ) denotes the magnitude of cytotoxicity [(-): no cytotoxicity, and (±): less cytotoxicity].

Acute Toxicity Testing

The compounds to be tested in the form of a 2% aqueous solution of Tween 80 were orally administrated to ICR male mice (weights: 24-30 g), five for each group. Over seven days after the administration of the compounds, they were observed in terms of in what conditions they were and measured in terms of weight. Table 4 shows the results of the $LD_{50}$ values found by the Litchfield-Willcoxon method.

Table 4

| Compounds | $LD_{50}$ (mg/kg) |
|---|---|
| Comp. Ex. 25 | >1000 |
| 37 | >1000 |

In Vivo Antiviral Action

BALB/c male mice of three weeks old, 10 for each group, were abdominally seeded with an infectious amount, $10LD_{50}$, of HSV-1(Miyama strain). One hour later and over six days after the next day, once a day, Compound (5) referred to in Table 1 was continuously administrated to each animal via an abdominal route. The results are set out in Table 5.

Table 5

Effect of Compound (5) on the Prolongation of Life of Mice Infected with HSV-1

| Dose (mg/Kg) | Mean Survival Days (average ± standard error) |
|---|---|
| Control | 6.1±0.6 |
| Table 1, Comp. (5) | 7.9±1.1 |
| (10) | 8.6±0.7* |
| (20) | 11.2±1.1*** |

t-Test

*: $p<0.05$, and ***: $p<0.001$

In Vitro Antiviral Action against Influenza Virus

For incubation, the compounds to be tested and influenza viruses (A/PR/8 strain) were added to monolayers of MDCK cells (epthelial cells derived from a canine kidney) grown. After incubation, the cytopathic effect (CPE) of the viruses as well as the effect of the compounds on CPE inhibition and on their cytotoxicity were microscopically observed. To assay the antiviral action of the compounds, $TCID_{50}$ values were found using the CPE as an index and $\Delta TCID_{50}$ ($log_{10}$) values were calculated by the $TCID_{50}$ values of both the compound-treated group and the control group. Bear in mind that prior to being added to the incubation systems, the compounds were mixed with ethanol or media to 20 mg/ml concentrations and diluted with media.

Table 6

Antiviral Action of Compounds against Influenza Viruses (A/PR/8 strain)

| Comp. Concn. (μg/ml) | Antiviral Activity ($\Delta TCID_{50}$ ($log_{50}$)) 1 | 5 | 20 |
|---|---|---|---|
| Table 1, Comp. (5) | 0.8 (-) | 1.2 (-) | 2.1 (-) |
| (9) | 0.5 (-) | 1.0 (-) | 1.3 (±) |
| (13) | 0.4 (-) | 0.6 (-) | 1.5 (±) |
| Ribavirin | 0.8 (-) | 1.8 (-) | 3.2 (-) |

Investigation was made with MDCK cells. ( ) stands for the magnitude of cytotoxicity [(-): no cytotoxicity, and (±) less cytotoxicity].

Example I of Formulation (Capsule)

A capsule was conventionally prepared according to the following recipe.

| | |
|---|---|
| Compound Ex. 25 | 250 mg |
| Magnesium stearate | 5 mg |
| Lactose | suitable amount |
| | Total: 300 mg |

Example II of Formulation (Tablet)

A tablet was conventionally prepared wtih a suitable vehicle according to the following recipe.

| | |
|---|---|
| Compound Ex. 37 | 250 mg |
| Sodium lauryl sulfate | 10 mg |
| Magnesium stearate | 5 mg |
| Polyvinyl pyrrolidone K30 | 11 mg |
| Carboxymethylcellulose (Ca) | 7 mg |
| Lactose | 60 mg |
| Corn starch | suitable amount |
| | Total: 360 mg |

Example III of Formulation (Ointment)

Ointment conventionally prepared according to the following recipe was packed in an aluminium tube.

| | |
|---|---|
| Compound Ex. 25 | 3 g |
| White petroleum jelly | suitable amount |

Example IV of Formulation (Hydrogel)

A hydrogel preparation conventionally made according to the following recipe was packed in an aluminium tube.

| | |
|---|---|
| Compound Ex. 37 | 3.0 g |
| Hydroxypropylmethylcellulose | 0.1 g |
| Polysorbate 60 | 0.1 g |
| Gelatin | 0.5 g |
| 70% Sorbitol solution | 2.0 g |
| Citric acid | 0.1 g |
| Disodium hydrogen phosphate | 0.3 g |
| Sodium chloride | 0.5 g |
| Benzalkonium chloride | 0.02 g |
| Purified water | suitable amount |
| | Total: 100 g |

Example V of Formulation (Oral Ointment)

Ointment conventionally made according to the following recipe was packed in an aluminium tube.

| | |
|---|---|
| Compound Ex. 25 | 0.3 g |
| Carboxymethylcellulose (Ca) | 3.1 g |
| Liquid paraffin | 3.1 g |
| White vaseline | 1.2 g |
| Plastic base | suitable amount |
| | Total: 10 g |

Example VI of Formulation (Suppository)

| | |
|---|---|
| Compound Ex. 25 | 250 mg |
| Tannic acid | 30 mg |
| Ichthammol | 300 mg |
| Cacao butter | suitable amount |
| | Total: 1000 mg |

Example VI of Formulation (Eye Ointment)

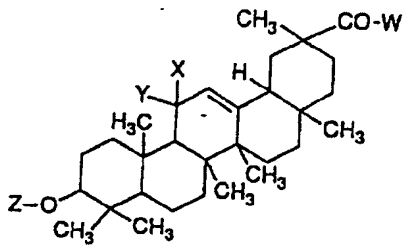
Eye ointment conventionally made according to the following recipe was packed in an aluminium tube.

| | |
|---|---|
| Compound Ex. 37 | 0.3 g |
| Liquid paraffin | 1.0 g |
| White petroleum jelly | suitable amount |
| | Total: 10.0 g |

The novel glycyrrhetinic acid derivatives according to this invention have an improved antirival action and so show excellent effects on the prophylaxis and treatment of a wide spectrum of DNA virus, RNA virus and retrovirus infections. The compounds of this invention are much wider in action spectra and much stronger in action than conventional antiviral drugs. In addition, these compounds are quite different in chemical structure from antiviral agents chiefly made up of a nucleic acid type compounds and now clinically used in the art, so that they can be efficacious against infections due to viruses resistant to these antiviral drugs.

## Claims

1. A glycyrrhetinic acid derivative having the following general formula (I):



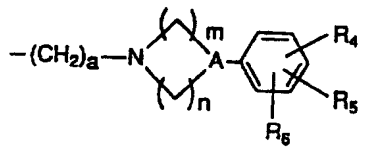
... (I)

where

X and Y each represent a hydrogen atom or forms together an oxo group,

Z represents $A_2$-$(CH_2)_n$-$(CH{=}CH)_m$-$A_1$-, wherein $A_1$ means a hydrogen atom or methylene or carbonyl, and $A_2$ means a hydrogen atom, a cyano group, a carbamoyl group, a carbonyl group or an alkoxycarbonyl group, m represents zero or an integer of 1-3, and n represents zero or an integer of 1-5, or a monosaccharide, disaccharide, oligosaccharide or polysaccharide or their derivative, and

W represents a substituent expressed by $-OR_1$ where $R_1$ means a hydrogen atom, an alkyl, substituted alkyl or substituted alkenyl group, or a group having the following general formula (II):

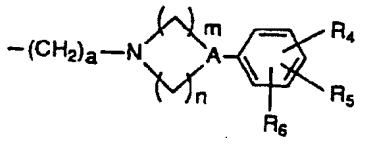


... (II)

wherein A means a nitrogen atom or a methyne or methylene group, and $R_4$, $R_5$ and $R_6$ concurrently or independently mean a hydrogen atom, an amino group, an optionally substituted alkylamino group, an acylamino group, an optionally substituted alkyl group, a hydroxy group, an optionally substituted alkyloxy group, a halogeno group, a carboxy group, a formyl group, an optionally substituted alkylcarbonyl group, an optionally substituted alkoxycarbonyl, an aryloxycarbonyl group, an optionally substituted carbamoyl group, a nitro group, a cyano group, a thiol group, an optionally substituted alkylthio group, an optionally substituted phenyl group or an optionally substituted heterocycle, m represents 0 or any desired integer, a and n each represent any desired integer, provided that the term "optionally substituted" means that said groups may be substituted by groups selected from amino, formyl, hydroxy, alkoxy, aryloxy, halogeno, nitro, cyano, thiol, alkylthio, arylthio, acyl, carbamoyl, alkylsilyl, arylsilyl, alkyloxycarbonyl, aryloxycarbonyl,

alkylsulfonyl, arylsulfonyl, alkylsulfinyl and arylsulfinyl groups, such acid groups as phosphoric, phosphonic, phosphinic, phosphenic, sulfonic, sulfinic, sulfuric and boric acid groups or their esters, and the term "heterocycle" means pyridine, piperidine, piperazine, pyrrole, pyrrolidine, oxazole, imidazole, morpholine, diazole, triazole, tetrazole, thiazole or thiaziazole, which may be condensed with benzene or each other,

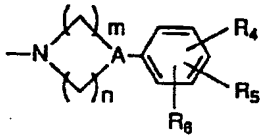
a substituent represented by $-NR_2R_3$ wherein $R_2$ and $R_3$ concurrently or independently represent a hydrogen atom, an alkyl, substituted alkyl or substituted alkenyl group, or a substituent having the general formula (III):



... (III)

wherein A, $R_4$, $R_5$, $R_6$, a, m and n have the same meanings as defined above,

a substituent represented by the following general formula (IV):



... (IV)

wherein A, $R_4$, $R_5$, $R_6$, m and n have the same meanings as defined above, or

a substituent represented by the following general formula $-NH-(CH_2)_a-A_3-R_7$ wherein a has the same meanings as defined above, $A_3$ denotes S, O or NH, and $R_7$ indicates an alkyl, alkenyl, phenyl or substituted phenyl group, or its salt.

2. 1-(3β-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine or its salt.

3. 1-(3β-(β-D-glucopyranosyloxy)-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine or its salt.

4. 1-(3β-(β-D-glucopyranosyloxy)-11-oxo-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine or its salt.

5. 1-(3β-(β-D-glucopyranosyloxy)-18β-olean-12-en-30-oyl)-4-(2-chlorophenyl)piperazine or its salt.

6. 1-(3β-(β-D-glucopyranosyloxy)-11-oxo-18β-olean-12-en-30-oyl)-4-(2-chlorophenyl)piperazine or its salt.

7. 1-(3β-(β-D-glucopyranosyloxy)-18β-olean-12-en-30-oyl)-4-(2-trifluoromethylphenyl)piperazine or its salt.

8. 1-(3β-(β-D-glucopyranosyloxy)-11-oxo-18β-olean-12-en-30-oyl)-4-(2-trifluoromethylphenyl)piperazine or its salt.

9. 1-(3β-(β-D-glucopyranosyloxy)-18β-olean-12-en-30-oyl)-4-(2,6-dichlorophenyl)piperazine or its salt.

10. 1-(3β-(β-D-glucopyranosyloxy)-11-oxo-18β-olean-12-en-30-oyl)-4-(2,6-dichlorophenyl)piperazine or its salt.

11. 3β-(β-D-glucopyranosyloxy)-N-(2-(4-(2-methoxyphenyl) piperazine-1-yl)ethyl)-18β-olean-12-en-30-amide or its salt.

12. 3β-(β-D-glucopyranosyloxy)-N-(2-(4-(2-methoxyphenyl) piperazine-1-yl)ethyl)-11-oxo-18β-olean-12-en-30-amide or its salt.

13. 3β-(β-D-glucopyranosyloxy)-N-(2-(4-(2-chlorophenyl) piperazine-1-yl)ethyl)-18β-olean-12-en-30-amide or its salt.

14. 3β-(β-D-glucopyranosyloxy)-N-(2-(4-(2-chlorophenyl) piperazine-1-yl)ethyl)-11-oxo-18β-olean-12-en-30-amide or its salt.

15. 30-((4-(2-methoxyphenyl)piperazine-1-yl)carbonyl)-18β-olean-12-en-3β-yl-2-O-β-D-glucuronyl-α-D-glucuronic acid or its salt.

16. 3β-O-(2,4,6-tri-O-sulfonate)-β-D-glucopyrasyl-11-oxo-18β-olean-12-3n-30-oic acid or its salt.

17. 3β-carboethoxy-18β-olean-12-en-30-oic acid or its salt.

18. 1-3(β-hydroxy-18β-olean-12-en-30-oyl)-4-(2-methoxyphenyl)piperazine or its salt.

19. 1-[3β-(3-carboxy-cis-propenoyloxy]-18β-olean-12-en-30-oyl]-4-(2-methoxyphenyl)piperazine or its salt.

20. 1-[3β-(3-carboxypropanoyloxy)-18β-olean-12-en-30-oyl]-4-(2-methoxyphenyl)piperazine or its salt.

21. N-[2-(3,7,11-trimethyl-2,6,10-dodecatorien-1-ylthio)ethyl]-3β-(3-carboxy-cis-propenoyloxy)-11-oxo-18β-olean-12-en-30-amide or its salt.

22. 1-[3β-(3-carboxy-cis-propenoyloxy]-11-oxo-18β-olean-12-en-30-oyl]-4-(2-methoxyphenyl)piperazine or its salt.

23. 1-[3β-(3-carboxy-propanoyloxy]-18β-olean-12-en-30-oyl]-4-(3,7,11-trimethyl-2,6,10-dodecatorien-1-yl)-piperazine or its salt.

24. An antiviral composition containing as a main active component a compound or its salt as claimed in any preceding claim especially as claimed in any one of Claims 17-23.

25. An antiviral composition as claimed in Claim 24, which further contains a polyoxyethylene higher alcohol ether or a surface active material.

26. Use of an antiviral composition as claimed in Claims 24 or 25 for the prophylaxis and treatment of infections induced by various DNA, RNA and retro-viruses.

27. Use of an antiviral composition as claimed in Claims 24 or 25 for the prophylaxis and treatment of of herpes virus infections.

28. Use of an antiviral composition as claimed in any one of Claims 24 or 25 for the prophylaxis and treatment of influenza virus infections.

European Patent Office

# EUROPEAN SEARCH REPORT

Application Number

## DOCUMENTS CONSIDERED TO BE RELEVANT

EP 92304934.0

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.5) |
|---|---|---|---|
| X | PATENT ABSTRACTS OF JAPAN, unexamined applications, section C, vol. 13, no. 42, January 30, 1989 THE PATENT OFFICE JAPANESE GOVERNMENT page 48 C 565 * Kokai-no. 63-243 093 (FUJIREBIO INC) * -- | 1,24, 26 | C 07 H 15/256<br>C 07 C 61/29<br>C 07 C 61/35<br>C 07 C 69/753<br>C 07 C 235/40<br>A 61 K 31/70 |
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| X | GB - A - 2 122 893 (BIOREX LABORATORIES LIMITED) * Page 1, lines 16-32 * -- | 1,24, 27 | TECHNICAL FIELDS SEARCHED (Int. Cl.5)<br>C 07 H<br>C 07 C 61/00<br>C 07 C 69/00<br>C 07 C 235/00<br>A 61 K |
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| A | DE - A - 2 711 081 (BIOREX LABORATORIES LIMITED) * Examples 8,9 * | 1 | |

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| VIENNA | 08-09-1992 | SCHNASS |

CATEGORY OF CITED DOCUMENTS

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TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
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| VIENNA | 08-09-1992 | SCHNASS |

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